

REVIEW ARTICLE

Hereditary Nonpolyposis Colorectal Cancer (HNPCC)/Lynch Syndrome

Verena Steinke, Christoph Engel, Reinhard Büttner, Hans Konrad Schackert, Wolff H. Schmiegel, Peter Propping

SUMMARY

Background: Hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) is a genetic disease of autosomal dominant inheritance. It is caused by a mutation in one of four genes of the DNA mismatch repair system and confers a markedly increased risk for various types of cancer, particularly of the colon and the endometrium. Its prevalence in the general population is about 1 in 500, and it causes about 2% to 3% of all colorectal cancers. Lynch syndrome is diagnosed in two steps: If it is suspected (because a patient develops cancer at an unusually young age or because of familial clustering), the tumor tissue is analyzed for evidence of deficient mismatch repair (microsatellite instability, loss of mismatch repair protein expression). If such evidence is found, a genetic mutation is sought. The identification of a pathogenic mutation confirms the diagnosis in the patient and enables predictive testing of other family members. Diagnostic evaluations for Lynch syndrome should be carried out with appropriate genetic counseling.

Method: Selective literature review.

Results: Prospective cohort studies from Germany, Finland and the Netherlands have shown that colorectal cancers detected by systematic colonoscopic surveillance tend to be at an earlier stage than those that are discovered after the patients present with symptoms. The Finnish study also showed an overall reduction in cancer risk from colonoscopic polypectomy at regular intervals.

Conclusion: The studies conducted so far have not yet clearly documented the putative benefit of an individualized, risk-adapted surveillance strategy. Until this is done, patients with Lynch syndrome and healthy carriers of causative mutations should be monitored with annual colonoscopy and (for women) annual gynecological examination.

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Until the 1980s it was assumed that hereditary factors played no role in common cancers. Today, this premise is viewed in a more nuanced light. On the one hand, there are known genetic risk factors for many common cancers, and on the other a range of hereditary tumor syndromes are known to be caused by a single, highly-penetrant genetic alteration or mutation and associated with a substantially increased risk of certain tumors. Hereditary tumors pose particular challenges for clinical, genetic, and pathological evaluation and require specific screening measures (1).

It is thanks to the American oncologist Henry T. Lynch that a hereditary form of colorectal cancer has been described and has been worked on for many years (2). The genetic basis of hereditary nonpolyposis colorectal cancer (HNPCC) has been elucidated in an impressive Finno-American collaboration (3–5). Research into HNPCC and improved diagnosis and patient care have gone hand in hand. Many cases of HNPCC syndrome result from autosomal dominant genetic mutations in one of four DNA mismatch repair (MMR) genes. Approximately one in 500 members of the general population carries a pathogenic mutation in an MMR gene, and the most common genetic predisposition to cancer overall is to HNPCC.

On the one hand, this article describes the current status of diagnosis and care for patients with HNPCC and those at risk. On the other, it presents the available data on the effectiveness of screening for HNPCC.

Defining HNPCC syndrome

Unlike familial adenomatous polyposis (FAP), HNPCC syndrome usually involves only single colorectal adenomas or carcinomas that cannot be clinically distinguished from sporadic tumors. Clinical and familial criteria have therefore been defined to identify patients with HNPCC. Patients who meet the Amsterdam Criteria (*eBox 1*) are HNPCC patients by definition (6, 7). Currently the Amsterdam Criteria also still cover families with no evidence of a DNA repair defect in a tumor, in which the increased tumor risk is probably due to genetic causes that have not yet been identified. The familial nature of colon cancer is also caused, to an unknown extent, by simple coincidence. HNPCC patients also include those who meet the weaker criteria of the Bethesda Guidelines (8, 9) (*Box 1*) and have a

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BOX 1

Amsterdam II Criteria and Revised Bethesda Guidelines

Amsterdam II Criteria (7)

● **All criteria must be met:**

- Three or more relatives with histologically confirmed colorectal cancer or cancer of the endometrium, small bowel, ureter, or renal pelvis, one affected relative being a first-degree relative of the other two; FAP should be excluded
- Two or more successive generations are affected
- At least one relative was diagnosed before the age of 50 years

Revised Bethesda Guidelines (8)

● **One or more of the following criteria must be met:**

- Colorectal cancer before the age of 50 years
- Synchronous or metachronous colorectal cancer or other HNPCC-related tumors^{*1}, regardless of age
- Colorectal cancer with MSI-high morphology^{*2} before the age of 60 years
- Colorectal cancer (regardless of age) and a first-degree relative with colorectal cancer or an HNPCC-related tumor before the age of 50 years
- Colorectal cancer (regardless of age) and two or more first- or second-degree relatives diagnosed with colorectal cancer or an HNPCC-related tumor (regardless of age)

^{*1} HNPCC-related tumors include colorectal, endometrial, stomach, ovarian, pancreas, ureter and renal pelvis, biliary tract, and brain (usually glioblastoma as seen in Turcot syndrome) tumors, sebaceous gland adenomas and keratoacanthomas in Muir–Torre syndrome, and carcinoma of the small bowel

^{*2} Presence of tumor-infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous/signet-ring cell differentiation, or medullary growth pattern
FAP: Familial adenomatous polyposis; HNPCC: hereditary nonpolyposis colorectal cancer; MSI: microsatellite instability

tumor with an MMR defect. The Bethesda Guidelines have a higher sensitivity but lower specificity than the Amsterdam Criteria regarding evidence of a mutation in an MMR gene. All patients carrying a cancer-causing germline mutation in an MMR gene (almost half of HNPCC patients) can also be said to have Lynch syndrome. However, in everyday clinical practice in Germany the terms “HNPCC” and “Lynch syndrome” are usually used synonymously.

Clinical presentation

HNPCC patients frequently develop colorectal cancer before the age of 50 (average age at onset of disease: 45 years), and approximately one-third of patients develop another HNPCC-typical tumor within 10 years (10). In addition, there is often an increased frequency of similar tumors in the patient's family (*eFigure*). If the Amsterdam Criteria or Bethesda Guidelines are met, molecular pathology testing of the cancer for alterations typical of HNPCC (testing for microsatellite instability [MSI] and MMR protein immunohistochemistry [IHC]) is indicated. For everyday clinical practice, we have developed a questionnaire that provides a simple way to obtain information according to the Revised Bethesda Guidelines (*Box 2*).

Colon cancers are the most common tumors in HNPCC patients, and approximately 2% to 3% of them are caused by a hereditary MMR defect (11). There is also a substantially increased risk of a range of other tumors (*Table*) (12–15). Endometrial carcinomas occur with a similar frequency to colon cancers in women with HNPCC. It is not uncommon for them to be

located in the uterus, so they may involve the cervix as adenocarcinomas. Although other tumors, such as breast cancers, bladder cancers, and prostate cancers, are observed somewhat more frequently in HNPCC patients than in the general population, they are not considered to be part of the typical HNPCC spectrum.

Because modern families are small, the penetrance of MMR mutations is incomplete, and individuals are often poorly informed about the diseases of their relatives, HNPCC is not always easy to identify. Bowel centers, surgeons, gynecologists, pathologists, and family doctors in particular have the important task of filtering out patients with suspected HNPCC.

Genetics

HNPCC patients' high risk of cancer is caused by a DNA repair defect due to a mutation in an MMR gene. As the mutation is usually inherited from one parent, every cell in the body initially carries both a defective copy of the gene and a fully functional copy that maintains DNA repair in cells. A cell develops a DNA repair defect only when its second copy of the gene also becomes nonfunctional (Knudson's two-hit hypothesis) as a result of a random mutation (somatic mutation). The DNA repair defect causes an increase in the frequency of somatic mutations in the cell line and therefore an acceleration of malignant degeneration. The dynamics of the formation of colorectal adenomas are probably an independent risk factor for the development of colon cancer in HNPCC patients (16).

Mutation analysis in MMR genes is performed when there is evidence of a DNA repair defect in a tumor.

BOX 2

**Questionnaire for determining the risk of familial colorectal cancer
(available at www.humangenetik.uni-bonn.de [in German])**

1. Have any of your first-degree relatives (parents, siblings, or children) been diagnosed with colorectal cancer?
2. Have you or any of your relatives been diagnosed with colorectal cancer before the age of 50?
3. Have you or any of your relatives been diagnosed with two cases of cancer, at the same time or one after the other, in any of the organs listed below^{*1}?
4. Is there someone in your family who has colorectal cancer and at least one other first-degree relative (parents, siblings, or children) who has been diagnosed with cancer in one of the organs listed below^{*1} before the age of 50?
5. Is there someone in your family who has colorectal cancer and at least two other relatives who have been diagnosed with cancer in one of the organs listed below^{*1}?
6. Have multiple polyps (adenomas) been found in the large intestine of any of your relatives, or has any of your relatives been diagnosed with polyposis?

^{*1} Large intestine, small intestine, stomach, womb (not cervix), ovaries, pancreas, bile ducts, ureter and renal pelvis, brain, sebaceous glands

● Evaluation

- Answer “No” to all questions: no increased risk of colorectal cancer, standard colorectal cancer screening
- Answer “Yes” to question 1 only: familial risk of colorectal cancer, more careful screening according to S3 Guideline
- Answer “Yes” to one or more of questions 2 to 6: suspected hereditary form of colorectal cancer, human genetic counseling recommended to provide further information

Mutations in individual MMR genes occur with varying frequency (Figure 1). Deletions in the *EPCAM* gene upstream of the *MSH2* gene can also cause HNPCC. The probability of identifying an MMR mutation in a patient depends heavily on family findings. Mutations in MMR genes whose consequences for the risk of cancer remain unclear (“unclassified variants”) are a major, and as yet unresolved, problem.

Mutations in the *MLH1* and *MSH2* genes have more effect on DNA repair than mutations in the other two MMR genes. Patients with an *MLH1* or *MSH2* mutation therefore have a substantially higher risk of tumors than patients with an *MSH6* mutation. The risk of patients with a *PMS2* mutation seems to be even lower than that of patients with an *MSH6* mutation. Because *PMS2* mutations are uncommon, little information is yet available on the risk of tumors. As with sporadic colon cancer, male germline mutation carriers have a higher risk of colon cancer than women with a mutation in the same gene (16).

In addition to mutations in these MMR genes, it is very likely that there are variants in other genes that increase the risk of colorectal cancer and partly explain the familial nature of colon cancer. Some of these variants are already known, but they seem to lead to only a small increase in risk. They are the subject of further research and as yet play no role in clinical diagnosis.

Pathology

HNPCC-related colon cancers are usually mucinous tumors that occur mainly in the right colon. Other

HNPCC-related tumors are also most of the times adenocarcinomas. Evidence of disrupted DNA repair in malignant cells includes lengthenings of short DNA replication sequences, known as microsatellites. Even though microsatellite instability (MSI) occurs in 10% to 15% of all colon cancers and 15% to 20% of all endometrial cancers, in combination with age at onset of disease and familial findings it is a strong predictor of Lynch syndrome. In families that meet the Amsterdam or Bethesda Criteria there is a 35% chance of finding microsatellite instability. A causal MMR mutation can be identified in 53% of families with microsatellite instability (authors' own figures).

Because altered proteins that are presented on the cell surface are also formed in cells as a result of repair weaknesses, an immune response to tumor cells is triggered. This takes the form of lymphocytic infiltrate in the tumor tissue. Immunohistochemical imaging shows evidence of a loss of the repair protein encoded by the affected gene in malignant tissue. Because the products of *MLH1* and *PMS2*, and *MSH2* and *MSH6*, each form a protein complex in cells, mutations in the *MLH1* gene, for example, lead to a loss of *MLH1* and its partner protein *PMS2* in immunohistochemical examination. Depending on the loss pattern, a human geneticist decides which MMR gene to perform a mutation analysis on. As assessment of immunohistochemical examination is heavily examiner-dependent, an additional microsatellite analysis should always be performed according to the recommendations of the German Society for Digestive and Metabolic Disorders

(DGVS, Deutsche Gesellschaft für Verdauungs- und Stoffwechselerkrankungen) (currently undergoing revision).

Loss of MLH1 and PMS2 can also occur in sporadic carcinomas. It is usually caused by *MLH1* promoter methylation in tumor tissue, resulting in functional deactivation of the *MLH1* gene. Possible causes of *MLH1* promoter methylation in colon cancer include certain somatic mutations in the *BRAF* gene that have occurred in tumor cells, particularly the V600E mutation. Because this mutation has not yet been observed in any patients with a pathogenic germline mutation in the *MLH1* gene, the presence of this mutation in a tumor is strong evidence that the tumor is non-hereditary (Figure 2). Recently a diagnostic procedure has been increasingly encouraged in which all colon cancers are tested for microsatellite instability, regardless of clinical criteria. This may increase the already high sensitivity of HNPCC patient detection still further (17). However, most MSI-positive colon cancers are not due to HNPCC. These are therefore false positives that must be followed up with expensive molecular genetic tests. It is not yet possible to rule out HNPCC reliably in this way, and this often leads to patients and treating physicians feeling uncertain. Testing all colon cancers for MSI would only become worthwhile if it gave rise to specific alterations to treatment. This is not yet the case.

Screening and prevention

Individuals with a pathogenic mutation in an MMR gene have a major increase in cancer risk throughout their lives. Even after successful oncological treatment, patients are at risk of other de novo cancers. A screening strategy has therefore been developed and is recommended to both HNPCC patients themselves and their at-risk family members (Box 3). The current screening recommendations in Germany have been incorporated into the S3 Guideline for colorectal cancer, which is currently being revised. They are very similar to European recommendations (18).

To date, there are prospective studies from Germany, Finland, and the Netherlands (with surveillance intervals of between one and three years) on which statements on the effectiveness of preventive colonoscopies can be based (16, 19–21). Because the adenoma–carcinoma sequence is also valid for HNPCC, it can be assumed that removing colorectal adenomas can reduce HNPCC patients' risk of cancer. On the basis of a small sample from the Finnish cohort in whom screening colonoscopies had already begun before the MMR genes were identified, Järvinen et al. (19) were indeed able to show that polypectomy had an effect in primary prevention, as the carcinoma rate was significantly reduced. The researchers had performed colonoscopies on a group with HNPCC at three-year intervals, while a second group that did not receive screening colonoscopies served as the control group. In a subsequent analysis, the same group even showed that the colorectal cancer mortality rate in genetic

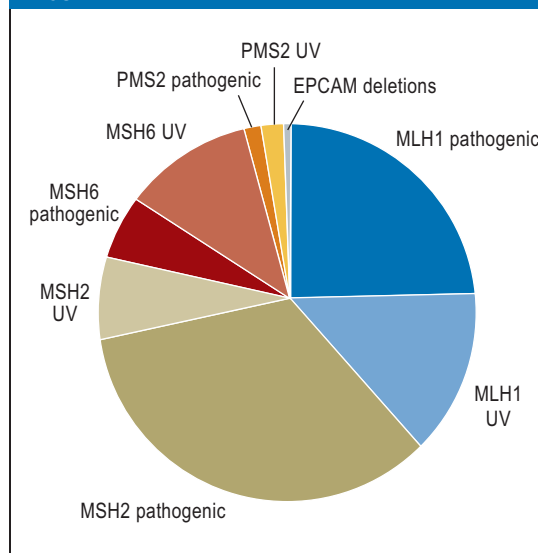
TABLE

Tumor spectrum and lifetime risks for HNPCC patients, general information for all MMR genes (data from the German HNPCC Consortium) (12–15)

Tumor	Risk in men	Risk in women
Colorectal cancer	34 to 73%	32 to 59%
Endometrial cancer	–	39 to 50%
Ovarian cancer	–	7 to 8%
Stomach cancer	1 to 6%	
Cancer of the renal pelvis/ureter	2 to 8%	
Cancer of the bile ducts	1 to 4%	
Cancer of the small bowel	1 to 4%	
CNS tumors	Approx. 2%	
Pancreatic cancer	Approx. 4%	
Tumors of the sebaceous glands (Muir–Torre syndrome)	Depends on affected gene	

HNPCC, hereditary nonpolyposis colorectal cancer

FIGURE 1



Mutations
according to the
German HNPCC
Consortium
UV, unclear variants)

carriers was no higher than in their relatives with no MMR mutations (20).

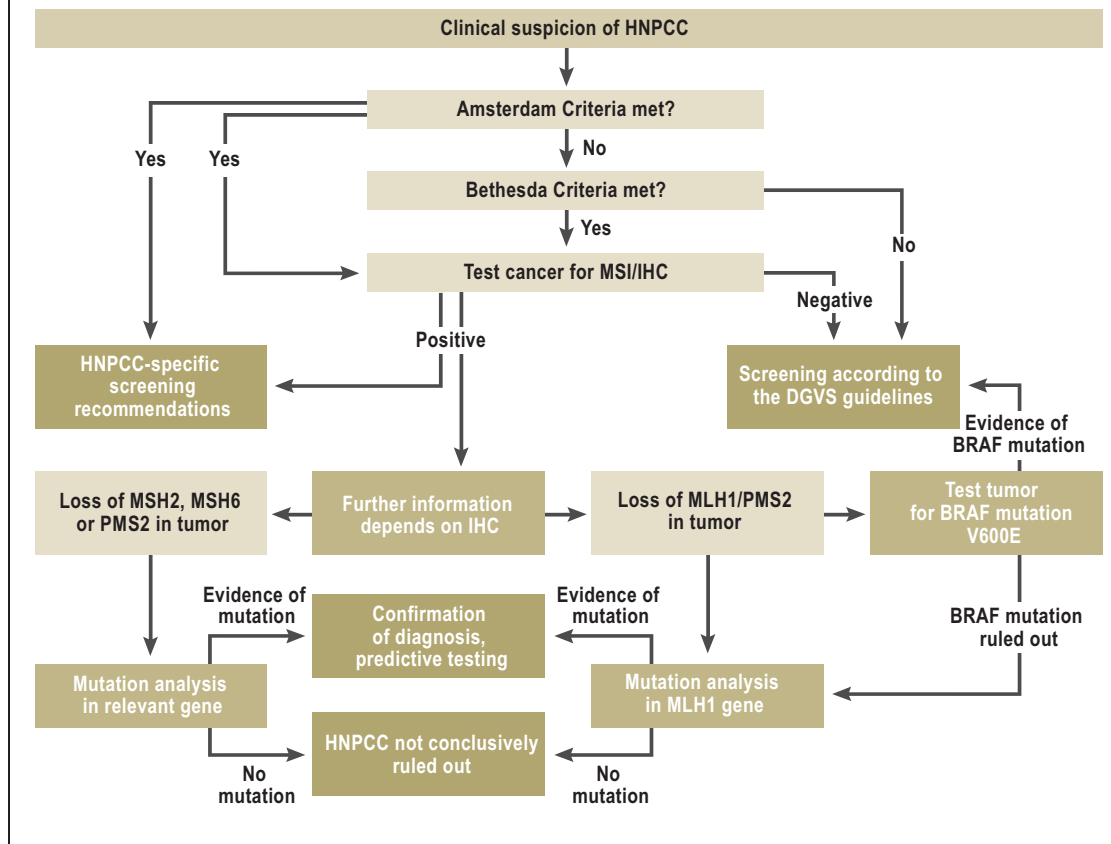
In the cohort of the German HNPCC Consortium, annual colonoscopies were recommended to study participants. Such frequent screening proved feasible and effective. Colorectal cancers detected at regular colonoscopies had a significantly more favorable staging than malignancies diagnosed symptomatically (16). Better prognosis may therefore be assumed.

In the Dutch cohort, the risk of cancer in HNPCC patients undergoing colonoscopies at one to two year intervals was lower than in patients undergoing them every two to three years (21).

Algorithms for the diagnosis of HNPCC

HNPCC, hereditary nonpolyposis colorectal cancer; DGVS, German Society for Digestive and Metabolic Disorders; MSI, microsatellite instability; IHC, immunohistochemistry

FIGURE 2



To date, a reduction in mortality rate has been reported only in the Finnish study, in which the number of cases was limited. In the German and Dutch cohorts, prospective observation periods are not yet long enough to determine an effect on survival with certainty. However, there is no doubt that frequent screening colonoscopies in MMR mutation carriers leads to more favorable staging of identified carcinomas and even reduces the rate of carcinomas. Nevertheless, the details of the results of the three prospective studies are inconsistent with each other. They cannot be used to decide on the best frequency of screening. HNPCC includes several disease entities, depending on which gene is mutated. This probably means that no single screening protocol is suitable for all MMR genetic carriers and persons at risk. Rather, the goal must be to develop a risk-adjusted screening strategy that takes into account the known differences in penetrance between mutated MMR genes and between the sexes and the dynamics of adenoma development. Until reliable data on this subject are available, the German HNPCC Consortium recommends annual screening (Box 3).

Colon cancers in HNPCC patients are also treated surgically, in line with surgical standards. There are no controlled studies available that address the question of whether radical surgery is appropriate. Any decision on

radical surgery, up to and including colectomy, would need to take into account the risk of surgery, the patient's age and sex, long-term medical prognosis, and the patient's expected compliance. It is also important to remember that the penetrance of MMR mutations is incomplete and that preventive adenoma removal has been shown to reduce the tumor risk.

Patients with microsatellite-unstable tumors have a better prognosis than those with stable tumors (probably due to an immune response to tumor cells). This means that there may be less benefit from adjuvant therapy. Several retrospective studies have shown that patients with microsatellite-unstable stage II and III colon cancer do not benefit from adjuvant 5-FU-based chemotherapy (22). Ongoing research is investigating whether this is also true of colon cancers in HNPCC patients.

Screening and prevention of other HNPCC-related tumors

Endometrial cancer is the second-most common tumor type in female HNPCC patients. Several studies have shown that transvaginal ultrasound (TVU) combined with endometrial biopsy is significantly more effective in early diagnosis of endometrial cancer than TVU alone (23, 24). As a result, endometrial pipelle biopsy

in addition to TVU is being recommended for female HNPCC patients aged over 35 in Germany, as is also encouraged internationally (18). In addition, after their family planning is complete, the option of prophylactic hysterectomy should be discussed with female carriers of an MMR mutation. To date there is no effective screening method for ovarian cancer, which is also more common in female HNPCC patients.

The literature contains little reliable information on screening for other HNPCC-related tumors (*Table*). The effectiveness of esophagogastroduodenoscopy (EGD) cannot yet be stated with certainty, due to the small number of examined cases. Because urine cytology, which used to be performed for urothelial cancer screening, showed very low sensitivity and a high number of false positives, it is no longer recommended. For other rare HNPCC-related tumors there are currently no specific screening measures other than abdominal ultrasound and general physical examination.

Care for patients and their families

According to Germany's Genetic Diagnostics Act, genetic evaluation for hereditary colorectal cancer can be arranged for patients by any physician, but patients must be offered human genetic counseling. The genetic counselor's job is not only to inform the patient of the clinical picture and genetic basis, but also to discuss with him or her which molecular genetic diagnostic procedure is appropriate.

Evidence of causal genetic alteration in a patient allows healthy relatives to undergo predictive genetic testing. Children and siblings of a genetic carrier have a 50% risk of carrying the same mutation due to autosomal dominant heredity. If predictive genetic evaluation provides evidence of a familial mutation, the relative should undergo screening. If the mutation can be ruled out, the relative does not have an increased risk of cancer and need not undergo special screening. According to the Genetic Diagnostics Act the person to be tested must undergo genetic counseling by a physician working in human genetics before predictive genetic evaluation is performed.

Far fewer than half of all genetic HNPCC carriers in Germany have been successfully identified to date. Physicians must always be aware of the increased risk of malignancy affecting many organs during long-term care of these patients. Patients should therefore be treated in facilities that offer a broad range of specialized care whenever possible, as is the case in the centers of German HNPCC Consortium (*eTable 2*).

Need for further research

HNPCC could become a frame of reference for risk-adjusted cancer screening. This requires results from further prospective studies. However, in Germany it is almost impossible to obtain research funding to perform the urgently required long-term clinical studies.

BOX 3

Screening Program for HNPCC Patients

Annual screening (age 25 onwards or beginning no later than 5 years before the lowest age of onset in family)

- Physical examination
- Abdominal ultrasound
- Full colonoscopy
- Gastroscopy (age 35 onwards)
- Gynecological examination including transvaginal ultrasound
- Endometrial pipelle biopsy (age 35 onwards)

HNPCC, hereditary nonpolyposis colorectal cancer

Conflict of interest statement

Between 1999 and 2011 the authors received funding from Deutsche Krebs-hilfe (German Cancer Aid), as part of the joint project *Familial Colorectal Cancer*.

Prof. Schackert has received lecture fees from the German Society for Digestive and Metabolic Disorders (DGVS, Deutsche Gesellschaft für Verdauungs- und Stoffwechselerkrankungen) and consultancy fees from the Medical Care Unit at University Hospital Dresden.

Prof. Schmiegel has received reimbursement of continuing education costs and travel expenses from the German Society for Digestive and Metabolic Disorders (DGVS, Deutsche Gesellschaft für Verdauungs- und Stoffwechselerkrankungen) and Falk. He has also received fees from Amgen, Apceth, Astra-Zeneca, Merck, Roche, Abbott, ECM, GSB, MedCongress, Pfizer, and Siemens Healthcare. Prof. Schmiegel holds several patents: PCT/DE2008/001220; DE102004063132.8-41; DE102006048249.2; DE102004036907.0-41; PCT/DE2007/002174; US61/176,353; DE102010046866.5; DE102011108254.2.

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KEY MESSAGES

- HNPCC (Lynch syndrome) is an autosomal dominant hereditary tumor syndrome caused by mutations in DNA mismatch repair system genes.
- Approximately one in 500 members of the general population carries a pathogenic mutation.
- The highest risks are for colorectal and endometrial cancers, but the risks of ovarian, stomach, ureter, bile duct, small bowel, and other cancers are also increased.
- Patients with Lynch syndrome and healthy mutation carriers should undergo annual screening colonoscopies and gynecological examinations.
- Findings from prospective cohort studies show that frequent screening colonoscopies are effective in early diagnosis and prevention.

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eBOX 1

Amsterdam I Criteria and Bethesda Guidelines

Amsterdam I Criteria (Vasen et al., 1991)

● **All criteria must be met:**

- Three or more relatives with histologically confirmed colorectal cancer, one affected relative being a first-degree relative of the other two; FAP should be excluded
- Two or more successive generations are affected
- At least one case of colorectal cancer was diagnosed before the age of 50 years

Bethesda Guidelines (Rodriguez-Bigas et al., 1997)

● **One or more of the following criteria must be met:**

- Positive family history according to the Amsterdam Criteria
- Synchronous or metachronous colorectal cancer or other HNPCC-related tumors (tumors of the endometrium, ovaries, stomach, bile ducts, small bowel, carcinoma of the ureter or renal pelvis)
- Colorectal cancer and a first-degree relative with colorectal cancer and/or an HNPCC-related extracolonic tumor (one of the cancers diagnosed before the age of 45 years) and/or colorectal adenoma diagnosed before the age of 40 years
- Colorectal or endometrial cancer diagnosed before the age of 45 years.
- Right-side, histologically undifferentiated colorectal cancer diagnosed before the age of 45 years
- Signet-ring cell colorectal cancer diagnosed before the age of 45 years
- Adenoma diagnosed before the age of 40 years

eBOX 2

German HNPCC Consortium

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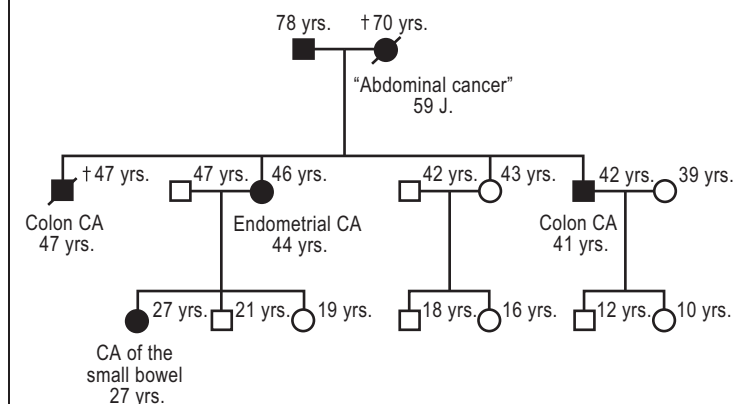
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eFIGURE



Genealogy of a family with HNPCC (CA, cancer)